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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	John B. Sullivan *et al.*
Serial No	:	08/405,454
Conf. No	:	6004
Filed	:	March 15, 1995
For	:	ANTIVENOM COMPOSITION CONTAINING FAB FRAGMENTS (As Amended)
Examiner	:	Ronald B. Schwadron
Art Unit	:	1644

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Commissioner for Patents
P.O. Box 1450
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Sir:

Transmitted herewith are the following documents:

- Amended Appeal Brief Under 37 C.F.R. § 1.192(b)(1)
- Return Receipt Postcard

If the enclosed papers are considered incomplete, the Mail Room and/or the Application Branch is respectfully requested to contact the undersigned at (617) 646-8000, Boston, Massachusetts.

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Respectfully submitted,
John B. Sullivan et al., Applicants

Respectfully submitted,

By: _____
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Docket No. P0786.90000US00
Filed: December 6, 2004

APPEAL BRIEF
-EXPEDITED PROCEDURE-
ART UNIT: 1644

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AMENDED APPEAL BRIEF UNDER 37 C.F.R. § 1.192 (b)(1)

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In response to the Notification of Non-Compliance with 37 C.F.R. § 1.192(c) mailed November 4, 2004, Appellants submit this Amended Appeal Brief.[1] As Examiner Schwadron indicated on November 29, 2004, by reflecting the Response and Amendment of November 3, 2004, this Amended Appeal Brief responds to the Notification of Non-Compliance.

I. Real Party in Interest

The real party in interest in the pending Appeal is the Assignee, Therapeutic Antibodies, Inc., by virtue of an Assignment from Appellants, duly recorded. Therapeutic Antibodies, Inc. has since merged with Proteus International, Inc. to form Protherics PLC.

II. Related Appeals and Interferences

Appellants, the undersigned, and the Assignee, know of no pending appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in this Appeal. As Appellants discuss more fully below, this application was subject to a previous appeal (Appeal No. 2001-1255; "the Previous Appeal") involving, *inter alia*, a § 103 rejection of previous versions of claims 40-42. In the Previous Appeal, the Board vacated the § 103 rejection of claims 40-42 but entered a new § 103 rejection of claims 40-42 over the same references.

III. Status of Claims

Claims 40-42, 50, and 54-55 are pending. Claims 54-55 stand withdrawn from consideration by the Examiner.[2] Claims 40-42 and 50 stand rejected by the Examiner under 35 U.S.C. § 103(a). The Appendix contains the pending claims on appeal—claims 40-42 and 50.

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[1] Because the original Appeal Brief was filed before the September 13, 2004 effective date of the Rules of Practice before the Board of Patent Appeals and Interferences (Final Rule) 69 Fed. Reg. 49959 (August 12, 2004), this Amended Appeal Brief follows the format of former 37 C.F.R. § 1.192 rather than current 37 C.F.R. § 41.37(c). *See* Clarification of the Effective Date Provision in the Rules of Practice before the Board of Patent Appeals and Interferences (Final Rule) 1287 O.G.66 (October 12, 2004) (Question 6).

[2] Claims 54-55 are method claims that multiply depend from product claims 40-42 and 50. Appellants would be entitled to present such claims after an indication of allowability of the product claims from which they depend. M.P.E.P. § 821.04 Rejoinder ("Where the application as originally filed discloses the product and the process for making and/or using the product, and only claims directed to the product are presented for examination, when a product claim is found allowable, applicant may present claims directed to the process of making and/or using the patentable product by way of amendment pursuant to 37 C.F.R. § 1.121.") As suggested by the MPEP, however, Appellants have already presented these claims rather than present them after an indication of

VI. Status of Amendments

Appellants filed concurrently with the original Appeal Brief an Amendment after Final Office Action requesting the cancellation of claims 51-53 and the amendment of claim 54 to reflect the cancellation of those claims. The Advisory Action and Notification of Non-Compliant Amendment mailed September 22, 2004 refused to enter the Amendment After Final Office Action because its claim listing did not include previously cancelled claims. After being informed of the docket clerk's failure to renumber the dependencies of claims 54-55 by Examiner Schwadron, Appellants filed a Response to Notice of Non-Compliant Amendment on November 3, 2004 amending claims 54-55 to depend from the proper claims. Examiner Schwadron indicated on November 29, 2004 that the Amendment, which included a complete claim listing, has now been entered. The Appendix reflects these amendments.

V. Summary of Invention

The claimed invention relates to an antivenom pharmaceutical composition for treating a snake bite victim. The antivenom pharmaceutical composition comprises Fab fragments that bind specifically to a venom of a snake of the Crotalus genus and that are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier. As the claims recite, the antivenom pharmaceutical composition for treating a snakebite victim neutralizes the venom of a snake of the Crotalus genus (claim 40). The source of the Fab fragments can be Ig(G)T (claim 41), the Ig(G)T can be polyvalent (claim 42), and the Fab fragments can be equine (claim 50).

An antivenom is a suspension of venom neutralizing antibodies that are prepared from the serum of animals that are hyperimmunized against a specific venom or venoms. [Specification at p. 4, lines 19-22.] Typically, animals are repeatedly injected with increasing doses of venom, and the animals' sera are collected and used to obtain antibodies that can neutralize the venom. Antivenoms are typically used to treat human snake bite victims. [*Id.* at p. 23, lines 1-3.]

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allowability of the product claims. *See id.* ("In view of the rejoinder procedure, and in order to expedite prosecution, Appellants are encouraged to present such process claims, preferably as dependent claims, in the application at an early stage of prosecution. ")

An antibody molecule is commonly referred to as an immunoglobulin (Ig) and is shaped like a "Y". [*Id.* at p. 2, lines 25-27.] The two upperarms of this "Y" contain the two antigen-binding sites of the antibody molecule. Exposing an antibody molecule to the enzyme pepsin results in the two upper arms of this "Y" splitting from the stem of the molecule but remaining attached to each other. This results in one $F(ab)_2$ fragment (the two upper arms—(and their two antigen-binding sites—attached to each other) and an Fc fragment (the stem). [*Id.* at lines 27-31.] Exposing an antibody molecule to the enzyme papain results in the two upper arms of this "Y" splitting both from the stem of the molecule and from each other. [*Id.* at lines 41-43.] This results in two separate Fab fragments (the two upper arms—thus, two separate antigen-binding sites) and an Fc fragment (the stem). [*Id.* at lines 27-31.] [3]

In the absence of any intervention to digest an antibody molecule into fragments, it exists in nature as the complete "Y", with the two antigen binding sites and the Fc stem. [*Id.* at p.2, lines 25-27.] Antibody molecules evolved this way to achieve several properties, including the ability to have any large molecular weight targets they bind phagocytized and eliminated by lymphocytes. [*Id.* at p. 3, lines 17-21.] Fab fragments, in contrast, cannot perform this function. Accordingly, before Appellant's invention, those of ordinary skill in the art thought Fab fragments would be of limited use against large molecular weight toxins—like snake venom toxins—because the Fab fragments could not cause them to be phagocitized and eliminated from the patient by lymphocytes. [*Id.* at p. 3, lines 21-23.] Contrary to this belief of those of ordinary skill in the art, Appellants discovered that an antivenom comprising Fab fragments had "far greater" antivenom activity than an antivenom of whole antibodies. [*Id.* at p. 10 lines 14-21.]

VI. Issues

Whether the Examiner properly made the following rejections:

A. rejection of claims 40-42 and 50 under 35 U.S.C. § 103(a) as being unpatentable over Sullivan *et al.* in view of Coulter *et al.* [Paper No. 48 at p. 4 (item 5)] and

B. rejection of claims 40-42 and 50 under 35 U.S.C. § 103(a) as being unpatentable over Sullivan *et al.* in view of Coulter *et al.* and Smith *et al.* as evidenced by Stedman's Medical Dictionary [Paper No. 48 at p. 5 (item 9)].

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[3] Antivenoms are also known as "antivenins," and $F(ab)_2$ fragments are also know as $F(ab')_2$ fragments.

VII. Grouping of Claims

Claims 40-42 and 50 stand or fall together concerning both the rejection under 35 U.S.C. § 103(a) over Sullivan *et al.* in view of Coutler *et al.* and the rejection under 35 U.S.C. § 103 over Sullivan *et al.* in view of Coutler *et al.* and Smith *et al.* as evidenced by Stedman's Medical Dictionary for purposes of this Appeal only.

VIII. Argument

The issues in this appeal arise directly from the Board's decision in the Previous Appeal. The Board's decision in the Previous Appeal regarding the two § 103 rejections over Sullivan *et al.* in view of Coulter *et al.* turned on whether or not the claims required a pharmacological activity. Thus, the Board affirmed the § 103 rejections of claims 45-47, which were directed to Fab fragments, but the Board vacated the § 103 rejections of claims 40-42, which were directed to an "antivenom composition" comprising Fab fragments.

While the Board vacated the rejection of claims 40-42, it believed "both the examiner and appellants place far too great a weight on the term 'antivenom' in the preamble of the claimed composition." [Paper No. 46 at p. 7.] Thus, the Board entered a new ground of rejection for claims 40-42 under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan *et al.* in view of Coulter *et al.* [Paper No. 46 at pp. 9-10.] Specifically, the Board asserted that the combination of Sullivan *et al.* in view of Coulter *et al.* taught all the elements of claim 40. [Paper No. 45 at pp. 9-10.]

The new ground of rejection was based upon the Board's belief that the mere recitation of an "antivenom composition" in the preamble did not result in the claims requiring a pharmaceutical activity. "There is no requirement in this claim that the Fab fragments exhibit a pharmaceutical activity." [Paper No. 45 at p. 9.] Because the Board did not believe claims 40-42 required a pharmaceutical activity, it concluded one of ordinary skill in the art would have combined Sullivan *et al.*'s IgG antivenom teachings with Coulter *et al.*'s teaching that Fab fragments improve the sensitivity of enzyme immunoassays (EIAs) "for use in EIAs to detect said venom." [Paper No. 46 at p. 9.] In other words, the Board believed that the combination of Sullivan *et al.* and Coulter *et al.* would have suggested using Fab antivenom fragments to **detect** Crotalus venom, not to **treat** envenomation with Crotalus venom.

Appellants subsequently amended the preamble of claim 40 to expressly recite that the antivenom composition is an "antivenom pharmaceutical composition for treating a snakebite victim." Moreover, Appellants also amended the body of claim 40 to recite that the antivenom pharmaceutical composition "neutralizes the lethality of the venom of a snake of the Crotalus genus." These amendments are illustrated below:

> 40. (Previously amended) An antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier, wherein said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the Crotalus genus.

Thus, there can be no doubt that this claim (as well as the remaining claims, which are similarly amended) now contains a "requirement . . . that the Fab fragments exhibit a pharmaceutical activity." [Paper No. 45 at p. 9.] The very basis of the Board's new ground of rejection in the Previous Appeal has therefore been removed.

Despite these amendments to claim 40 to specifically require that the antivenom pharmaceutical composition exhibits a pharmaceutical activity (specifically, neutralizes the lethality of the venom of a snake of the Crotalus genus), the Examiner maintained the rejection. In doing so, the Examiner merely asserted that the amended preamble was no more limiting than the old preamble. [Paper No. 48 at p. 4.] The Examiner did not even address the new clause in the body of the claim reciting that the antivenom pharmaceutical composition "neutralizes the lethality of the venom of a snake of the Crotalus genus." Indeed, even in the second rejection under appeal, where the Examiner supplemented the Board's new ground with further secondary references, the Examiner addressed Appellants' arguments by referring to the Examiner's Answer in the Previous Appeal. [Paper No. 48 at p. 6.]

Appellants' amendments in response to the Previous Appeal require that the antivenom pharmaceutical composition exhibit a pharmaceutical activity. As appellants discuss in detail below, this requirement that the antivenom pharmaceutical composition for treating a snakebite victim comprising Fab fragments neutralizes the lethality of the venom of a snake of the Crotalus genus renders the claims patentable. Those of ordinary skill in the art would not have expected an antivenom comprising Fab fragments to neutralize the lethality of the venom. Rather, they would have expected it to increase the lethality of the venom.

Appellants emphasize that this is not a case of merely stating a new use for an obvious composition, which the Board in the Previous Appeal reminded the Examiner and Appellants does not render composition claims patentable. [Paper No. 46 at pp. 7, 9 (citing *In re Zierden*, 162 USPQ 102, 104 (CCPA 1969) and *In re Pearson*, 181 USPQ 641, 644 (CCPA 1974.] Rather, the claims recite terms that "define . . . some characteristic not found in [prior art]." *Pearson*, 181 USPQ at 644. Such terms can "be used to distinguish a new from [the prior art]." *Id.* That is what they do here.

Moreover, the *Zierden* and *Pearson* cases are not the most relevant cases to this appeal because they both concerned a § 102 rejections, not a § 103 rejection. *Zierden*, 162 USPQ at 104 (While the Examiner did not specify § 102 or § 103 as the basis of the rejection, the Appellant conceded that the statement of intended use was the only basis for distinguishing the claim from a single prior art reference.); *Pearson*, 181 USPQ at 644 (The Board treated the rejection as a § 102 rejection.). The Federal Circuit has explicitly distinguished such cases involving § 102 rejections of claims reciting a functional characteristic when a claimed invention is put to its intended use from cases involving § 103 rejections of such claims. While it is proper to require that a prior art reference under § 102 be shown to lack the recited functional characteristic, that inquiry is simply irrelevant for a § 103 rejection. *In re Mills*, 16 USPQ2d 1430, 1432-33 (Fed. Cir. 1990). A § 103 rejection requires a suggestion to combine references to achieve the recited functional characteristic. *Id.* at 1432. The mere fact that a reference could have been used to achieve the recited functional characteristic does not render a claim obvious in the absence of such a suggestion.

As Appellants discuss in detail below, amended independent claim 40 now recites such terms that define characteristics that patentably distinguish the claimed antivenom pharmaceutical composition from the antivenom composition of Sullivan *et al.* combined with the EIA detection reagent of Coulter *et al.* (as well as the additional secondary references). There was no suggestion in the prior art that Fab fragments could be used to create an antivenom pharmaceutical composition for treating a snakebite victim that would neutralize the lethality of the venom of a snake of the Crotalus genus. This lethality neutralization is not just an intended use of the claimed product. It is a required characteristic of the claimed product that distinguishes it from the prior art, which believed that Fab antivenom compositions would not only fail to neutralize the lethality of the venom of a snake of the Crotalus genus, but would

actually enhance the lethality. Accordingly, both rejections of claims 40-42 and 50 under 35 U.S.C. § 103(a) over Sullivan et al. in view of Coutler et al. should be reversed

A. Antivenoms Comprising Fab Fragments Were Expected To Be Ineffective

Appellants have submitted numerous references and the Declarations of Dr. Damon Smith, Dr. John B. Sullivan, and Findley E. Russell, M.D., Ph.D.[4], which prove that the claimed invention would not have been obvious because one of ordinary skill in the art would not have had a reasonable expectation of success. Indeed, Dr. Sullivan "and others questioned whether anti-venom F(ab)'s would be effective [antivenoms]." [Sullivan Decl. at ¶9.]

The only commercially available antivenom at the time of Appellants' invention for North American snakes of the Crotalus genus was Antivenin [Crotalidae] Polyvalent (equine origin) ("ACP"), which had been available since 1947. [First Russell Decl. at ¶ 20.] ACP suffered the serious problem suffered by other antivenoms of often causing serum sickness, an allergic reaction to the antivenom that is sometimes as dangerous as the venom. [First Russell Decl. at ¶ 21; specification at p. 4, lines 35-40.] Over 75% of envenomation patients who receive ACP suffer from serum sickness. [First Russell Decl. at ¶ 21.] This danger was so great that physicians could not administer this antivenom for some cases of envenomation, and ACP could only be obtained in a kit that also contained test serum for attempting to detect serum sickness. [*Id.*][5]

Because of the serious problem of serum sickness, extensive research had been performed on developing better antivenoms. [First Russell Decl. at ¶ 24.] None of these attempts were successful, and ACP remained the only commercially available Crotalus antivenom. In recognition of this long-felt need for an effective Crotalus antivenom that did not suffer from serum sickness, the FDA designated Appellant's CroFab product an orphan drug. [Ex. 5 attached to Amendment of January 17, 1995.] Moreover, to expedite approval of CroFab, the FDA provided an orphan drug grant to support its development. [Ex. 6. attached to Amendment of January 17, 1995.] These two actions by the FDA are persuasive objective evidence of the nonobviousness of Appellants' invention. *See ATD Corp. v. Lyall, Inc.*, 159 F.3d

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[4] Dr. John B. Sullivan, and Findley E. Russell, M.D., Ph.D are the named inventors, and they are the authors of the Sullivan et al. reference.

[5] Wyeth discontinued production of ACP a few months after the FDA approved Appellants' CroFab product. Accordingly, appellants us the past tense while Dr. Russell used the present tense.

534 (Fed. Cir. 1998) (Reversing obviousness determination where, "It was undisputed that the product met an unsolved need and was quickly adopted by the industry....").

At the time of Appellants' invention, it was generally believed that "given possession of the antibody active site, the smaller the antibody molecule, the better". [Specification at p. 3, lines 1-2.] Thus, much antivenom research focused on immunoglobulin fragments, which may not provoke an immune reaction. [First Russell Decl. at ¶ 22.] In the late 1960's, researchers began experimenting with antivenoms comprising $F(ab)_2$ fragments, and such antivenoms first became commercially available outside the United States in 1969. [*Id.* at ¶ 25; Smith Decl. at ¶ 7.] Although the smaller size of the $F(ab)_2$ fragments results in less serum sickness, such antivenoms appeared less effective than antivenoms comprising whole immunoglobulin. [First Russell Decl. at ¶ 25.] Consequently, Crotalidae antivenoms comprising $F(ab)_2$ fragments were not produced in the United States. [First Russell Decl. at ¶ 24].

Although serum sickness had long been recognized as a major problem with antivenoms, and although smaller antibody fragments had long been known to be less immunogenic, no researcher developed antivenoms comprising the smaller Fab fragments before Appellants' invention. [*Id.* at ¶ 25; Sullivan Decl. at ¶ 5.] Indeed, there had been no significant improvements in commercial antivenoms since 1969, when an $F(ab)_2$ antivenom was commercially sold. [Smith Decl. at ¶ 7.] Development of antivenoms comprising antibody fragments halted at the larger $F(ab)_2$ fragments because researchers expected the smaller Fab fragments to be even less effective than $F(ab)_2$ fragments, which appeared to some to be less effective than whole antibody, for several reasons. [First Russell Decl. at ¶ 26; Sullivan Decl. at ¶ 5; Smith Decl. at ¶ 9.]

First, Fab fragments cannot stearically hinder the binding of a venom protein to its tissue target as well as $F(ab)_2$ fragments. The two binding sites on $F(ab)_2$ fragments allow them to bind to repeating antigenic determinants on large venom proteins, and this repetitive determinant binding stearically hinders the venom antigen from binding to its active site. [First Russell Decl. at ¶ 29; Sullivan Decl. at ¶ 8.] Because Fab fragments have only one active site [First Russell Decl. at ¶ 29; Sullivan Decl. at ¶ 8], they cannot stearically hinder by binding repetitive antigenic determinants.

Second, Fab fragments cannot cross-link venom proteins into complexes that precipitate like Fab_2 fragments can. $F(ab)_2$ fragments contain two antigen binding sites, so each individual

$F(ab)_2$ fragment can bind two antigens. [Steward Sell, *Basic Immunology: Immune Mechanisms in Health and Disease*, at p. 89, Fig. 6-3 (1987).] As more $F(ab)_2$ fragments cross-link more antigens, they form larger complexes that eventually become large enough that they precipitate from solution. *Id.* Because Fab fragments have only one antigen binding site, they cannot form cross-linked complexes and precipitate the antigens. [Smith Decl. at ¶ 9.]

Third, Fab fragments are cleared much more quickly than Fab_2 fragments—long before the venom. Many venom toxins are large, hydrophobic molecules, and they are usually injected deep into subcutaneous tissues. [First Russell Decl. at ¶ 30; Smith Decl. at ¶ 8.] These individual toxins are released slowly from the injection site, resulting in the "venom depot effect" whereby the venom toxins continue to be released into the circulatory system long after the initial bite. [First Russell Decl. at ¶ 30; Smith Decl. at ¶ 8.] Venom protein continues to be released from the injection site for weeks [Sullivan Decl. at ¶ 5(a)], and has been detected in a patient 46 days after envenomation. [Owenby *et al.*, *Southern Medical Journal* (1990).]

Fab fragments have a molecular weight of around 45-55 Kd. [First Russell Decl. at ¶ 31.] This relatively small size allows the renal system to remove Fab fragments, resulting in a half-life of about 17 hours. [*Id.*] Indeed, the renal system completely eliminates Fab fragments in only 24-26 hours. [*Id.*] $F(ab)_2$ fragments, in contrast, are too large for the renal system to remove them. [Id. at ¶ 32.] Thus, they have a much longer half-life than Fab fragments—approximately 50 hours versus approximately 17 hours. [*Id.*] Given the renal system's rapid removal of Fab fragments, those of ordinary skill in the art expected that there would be no remaining Fab fragments to neutralize later-released venom toxins. [*Id.* at ¶ 32; Smith Decl. at ¶ 8.]

For all these reasons, antivenoms comprising Fab fragments were expected to be ineffective in neutralizing the lethality of the venom of a snake of the Crotalus genus. Thus, despite the long-known, serious deficiencies of the only commercially available which long-felt need was recognized by the FDA, antivenom no researchers developed antivenoms comprising the smaller Fab fragments before Appellants' invention.

B. Antivenoms Comprising Fab Fragments Were Actually Expected to Be Harmful

Not only did those of ordinary in the skill in the art believe that Fab fragments would be ineffective in neutralizing the lethality of the venom of a snake of the Crotalus genus, they actually expected that such an antivenom "would **increase** the toxicity of the venom" by redistributing and concentrating its toxins. [Sullivan Decl. at ¶ 5(b) (original emphasis), ¶ 13; Russell Decl. at ¶ 33.] The binding of Fab fragments and venom toxins is a dynamic process, having an equilibrium where individual venom toxins are constantly bound and released. [First Russell Decl. at ¶ 34.] The renal system's rapid removal of Fab fragments, however, continually decreases the number of Fab fragments remaining to bind the venom toxins. [Smith Decl. at ¶ 8.]

Those of ordinary skill in the art were concerned that Fab fragments would bind venom toxins that were released into the circulatory system and then release the venom toxins at another site, perhaps concentrating the venom toxins in areas of high blood flow like the kidneys, heart, nervous system, and lungs. [First Russell Decl. at ¶ 36; Sullivan Decl. at ¶¶ 5(b), 11.] As Dr. Sullivan stated,

> I and others maintained and discussed our concerns that Fab [fragments] would redistribute toxic venom proteins throughout the body, thus producing venom pathology at tissue sites and organ systems not typically seen in patients treated with [whole antibodies] or $F(ab)_2$.

[Sullivan Decl. at ¶ 7.] While the toxins might have caused swelling and local necrosis at the site of envenomation, the predicted redistribution and concentration of venom toxins might result in "coagulopathy, direct cardiotoxicity, liver and kidney damage, potential central nervous system, and peripheral nervous system damage." [*Id.*] Thus, what had been a systemic toxicity with venom toxins being released slowly into the circulation could become a localized toxicity with venom toxins being concentrated in the kidneys, heart, nervous system, and lungs by this "taxi" effect. [First Russell Decl. at ¶ 36; Sullivan Decl. at ¶ 5(a).]

This taxi effect was a reason why those of ordinary skill in the art did not progress beyond the known $F(ab)_2$ fragments to the smaller Fab fragments. [Sullivan Decl. at ¶ 7.] According to Dr. Sullivan, the use of Fab fragments to treat envenomation would have been "medically unsound and contraindicated." [*Id.* at ¶ 13.]

The belief of those of ordinary skill in the art that Fab fragments would actually increase the lethality of a venom by concentrating high molecular weight snake toxins in areas of high blood flow was not merely a theoretical concern, as Faulstich *et al.* later demonstrated. Faulstich *et al.* "(Strongly Enhanced Toxicity of the Mushroom Toxin α-Amanitin by an Amatoxin-Specific Fab or Monoclonal Antibody," 26 *Toxicon* 491 (1988) (copy attached as Exhibit 7 to first Russell Declaration)] conducted a series of studies attempting to treat α-amatoxin poisoning with Fab fragments. Alpha-amatoxin is a high molecular weight toxin that is similar to some snake venom toxins. [First Russell Decl. at ¶ 37.] As a high molecular weight toxin, α-amatoxin cannot be cleared by the renal system. [*Id.*] Rather, it is cleared by the liver, like many snake toxins. [*Id.*] Since α-amatoxin is concentrated in the liver after oral ingestion, it is primarily toxic to liver cells. [*Id.*]

Faulstich *et al.* discovered that the Fab fragments did not decrease the toxicity of α -amatoxin in mice but rather **increased the toxicity** of α-amatoxin by a factor of 50. [Faulstich *et al.* at p. 497.] Furthermore, the Fab fragments resulted in α-amatoxin being specifically toxic to kidney cells rather than liver cells. [*Id.*] This is exactly what one of ordinary skill in the art would have predicted. [First Russell Decl. at ¶ 38.] The Fab fragments bound the high molecular weight α-amatoxin, and then unbound it in their state of equilibrium at sites of high blood flow. [*Id.*] This unbinding at sites of high blood flow, especially the kidneys, resulted in the α-amatoxin being concentrated in these tissues and killing them. [*Id.*] Thus, Fab fragments greatly increased the toxicity of this high molecular weight toxin by concentrating it in areas of high blood flow—the very concern of those who feared an Fab antivenom would actually increase venom toxicity.

Faulstich *et al.*'s results with Fab fragment directed to a **high** molecular weight toxin stand in contrast to Balthazar *et al.*'s results with Fab fragments to the **low** molecular weight toxin digoxin, a pharmaceutical sometimes ingested by children. [Balthazar *et al.* Utilization of Antidrug Antibody Fragments for the Optimization of Intraperitoneal Drug Therapy: Studies Using Digoxin as a Model Drug. *J. Pharm. Exp. Ther.* 268, 734 (1994) (attached at Exhibit 8 to the First Russell Declaration).] Digoxin is unlike most Crotalus venom toxins; it is a very small molecule, small enough that the renal system can clear the Fab-digoxin complex. [First Russell Decl. at ¶ 39; Smith Decl. at ¶¶ 8, 10.] Since the renal system can clear the Fab-digoxin complex, the Fab fragments did not redistribute and concentrate digoxin in areas of high blood

flow, just as one of ordinary skill in the art would have predicted. [First Russell Decl. at ¶ 39.] Accordingly, Balthazar *et al.* found that Fab fragments effectively treated digoxin toxicity, just as Smith *et al.*, upon which the Examiner also relies, found.

While Balthazar *et al.* effectively used Fab fragments to treat a small toxin, they recognized Fab treatment could actually have a deleterious effect for other toxins like the large α-amatoxin, as Faulstich *et al.* found:

> First, the alteration of drug distribution which accompanies antibody drug complexation may result in a **potentiation of drug toxicities** or the **development of new drug toxicities** in certain cases. For example, Faulstich *et. al.* (1988) have shown an enhancement of the renal toxicity of α-amantin (a mushroom toxin) when this toxin was coadministered with antiamantin immunoglobulin G and Fab fragments. This toxicity is presumed to result from an increased delivery of the toxin (as the anitbody-toxin complex) to protein-metabolizing cells of the kidney. The risk of **redistributing systemic toxicity**, rather than minimizing systemic toxicity, should be appreciated as a potential outcome of the proposed approach.

[Balthazar *et al.* at p. 738, cols. 1-2 (emphasis added).]

Accordingly, those of ordinary skill in the art were concerned that treating a snakebite victim with an antivenom comprising Fab fragments would actually be harmful because the Fab fragments would redistribute high molecular weight toxins to areas of high blood flow, creating new toxicities. Faulstich *et al.* confirmed this concern by showing that Fabs to a toxin that is of a similar molecular weight as many snake venom toxins increased toxicity. [First Russell Decl. at ¶ 41.] Balthazar *et al.* reinforced this concern by showing that this effect did not occur with a low molecular weight toxin whose Fab-toxin complex, the renal system could clear, while still discussing their concern that Fab fragments might increase or redistribute toxicities of large toxins. [First Russell Decl. at ¶ 42.]

C. The Cited References Would Not Have Motivated One of Ordinary Skill in the Art To Attempt the Claimed Invention

Against this evidence that those of ordinary skill in the art would not have expected an antivenom pharmaceutical composition comprising Fab fragments to neutralize the lethality of the venom of a snake of the Crotalus genus but would have actually expected it to increase the lethality, the Examiner apparently relies upon Coulter *et. al.*'s teaching that Fab fragments neutralized the lethal effects of textilotoxin [Paper No. 48 at pp. 4, 6] and Smith *et. al.*'s teaching

that Fab fragments may have therapeutic advantages in clearing digoxin. [Paper No. 48 at p.6.][6] Appellants will address each of these two alleged sources of motivation in turn.

1. **Coulter *et al.* would not have provided any motivation**

The same *in vivo* characteristics of Fab fragments that led those of ordinary skill in the art to expect that the claimed invention might actually increase the lethality of the venom of a snake of the Crotalus genus show that the Examiner's reliance upon the Coulter *et al.* reference for providing any motivation is misplaced. The Coulter *et. al.* article was published in the Journal of **Immunological Methods** and is entitled "**Simplified Preparation** of Rabbit Fab Fragments." Coulter *et. al.* were using Fab fragments as a tool to study textilotoxin binding sites and were seeking a simpler way to make them. [Coulter *et al.* at p. 199.] Thus, Coulter *et al.* did not treat envenomation with their Fab fragments.

Instead of treating envonomation, Coulter *et al.* tested the binding abilities of their Fab fragments in an enzyme immunoassay and in a mouse protection assay. [Coulter *et al.* at p. 201] In the mouse assay, Coulter *et al.* first mixed textilotoxin with their Fab fragments *in vitro*. [Coulter *et al.* at p. 201, 3rd full paragraph.] Coulter *et al.* then injected the **already bound Fab-textilotoxin complex** intravenously. This treatment with Fab fragments resulted in neutralization that was essentially equivalent to the treatment with the IgG fragments, just as one of ordinary skill in the art would have expected. [First Russell Decl. at ¶ 48.] Since the Fab-textilotoxin mixture was first mixed *in vitro* and then injected intravenously, the Fab did not have the opportunity to redistribute and concentrate the textilotoxin in high blood flow parts. [*Id.*] Accordingly, the Coulter *et al.* reference would not have provided a reasonable expectation of success for an antivenom comprising Fab fragments, despite the Examiner's assertion to the contrary. [*Id.*]

The inability to extrapolate Coulter *et al.'s in vitro* Fab results was not merely a theoretical concern, as Sorkine *et al.* later confirmed. Sorkine *et al.* conducted a similar experiment by mixing Fab fragments with a snake venom before injecting the mixture into a mouse, and they obtained similar results. [Sorkine *et al.*, "Comparison of $F(ab')_2$ and Fab Efficiency on Plasma Extravasations Induced *Viper aspis* Venom," Toxicon 33: 257 (1995) (attached as Exhibit 11 to the First Russell Declaration).] The Fab fragments were effective

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[6] Smith *et al.* is only relied upon in the second rejection under appeal.

when they were mixed with the venom before administration. However, the Fab fragments were much less effective when they were administered separately from the venom. [*Id.*] As Sorkine *et al.*, state "these data showed firstly that the *in vitro* neutralization of the venom by immunoglobulin fragments **does not reflect their *in vivo* efficiency**." [*Id.* (emphases added).] Thus, the Sorkine *et al.* reference shows that one would not have expected Coulter *et al.'s* **in vitro** neutralization results to predict the effectiveness of antivenoms comprising Fab fragments **in vivo**. [First Russell Decl. at ¶ 50.] Coulter *et al.*'s Fab fragments were not exposed to the **in vivo** mechanisms that taught away from the claimed invention.

One of ordinary skill in the art would not have found any motivation in Coulter *et al.* for the additional reason that Coulter *et al.* used textilotoxin, one of several toxins in the venom of the Australian brown snake (*Pseudonaja textilis*).[7] [Coulter *et al.* at p. 199, last sentence; First Russell Decl. at ¶ 46.] Although venoms can be simple substances, in snakes they are often very complicated mixtures of many individual toxins. [First Russell Decl. at. ¶¶ 15, 47; Smith Decl. at ¶ 6.] In some venoms of Crotalus snakes, there may be 100 different protein fractions. [First Russell Decl. at ¶ 15.] Due to their complexity, the full composition of snake venoms is unknown. [*Id.*] Not only is the composition of snake venoms complicated and their exact composition unknown, but the pharmacological effects of some constituent toxins are unknown. [*Id.* at ¶ 16.]

Due to the unknown composition of snake venoms and the unknown effect of even the identified toxins in snake venoms, basic toxicology texts caution against extrapolating results from individual venom toxins (like Coulter *et al.'s*) to whole venoms (like the claims recite). [*Toxic Effects of Animal Toxins* at p. 802; *Snake Venom Poisoning* at p. 168.] Accordingly, the Examiner is incorrect in attempting to extrapolate Coulter *et al.'s* results with Fab fragments to a single snake venom toxin to the results that would have been expected with Fab fragments to an entire snake venom. As Dr. Russell stated, "one would not have expected Coulter *et al.'s* results with Fab to a single **toxin** to predict similar results with Fab to . . . a Crotalus snake **venom**." [First Russell Decl. at ¶ 47 (original emphasis).] Since one of ordinary skill in the art would not

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[7] The pending claims recite a snake of the genus Crotalus, a genus of the family Crotalidae. As can be seen from its name, the snake Coulter *et al.* used is not a member of the genus Crotalus, nor is it even of the same family as the Crotalus genus. Rather, it is a member of the genus *Pseudonaja*. [Coulter *et al.* at p. 199.] Indeed, Coulter *et al.'s* snake is an elapid [Russell, "Toxic Effects of Animal Toxins," In *Casarett and Doull's Toxicology: The Basic Science of Poisons*, (5th Ed. 1996) at p. 802 (attached as Exhibit 10 to the First Russell Declaration)], and the elapids are of the family Elapidae, not Crotalidae. [*Snake Venom Poisoning* at p. 5.]

have expected Coulter *et al.*'s results with Fab fragments to a single venom toxin to predict what would occur with an antivenom comprising Fab fragments to an entire venom, any rejection relying upon the Coulter *et al.* reference must fail.

"Hindsight is not a justifiable basis on which to find" that an invention was obvious. *Amgen v. Chugai Pharm. Co. Ltd.*, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Rather, the prior art, not Appellants' disclosure, must have provided a reasonable expectation of success. [*Id.*] at 1022; *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Reliance upon Coulter *et al.*'s *in vitro* results with a single venom toxin, however, depends upon a hindsight-aided application of the teachings from Appellants' disclosure, not the prior art—one that basic toxicology test caution against making. In contrast to this hindsight, the evidence Appellants have submitted shows that this rejection fails for a lack of the required expectation of success.

2. Smith *et. al.* would not have provided any motivation

Smith *et. al.* would not have provided any motivation to attempt the claimed invention because, like the Balthazar *et. al.* article discussed above, Smith *et. al.* involved Fab fragments to the small molecule digoxin. As discussed above, digoxin is small enough that an Fab-digoxin complex can be cleared by the renal system. [First Russell Decl. at ¶ 39; Smith Decl. at ¶¶ 8, 10.] In contrast, many venom toxins are too large to be cleared by the renal system. [First Russell Decl. at ¶37.] Because an Fab–digoxin complex is cleared by the renal system, Smith *et. al.*'s statements concerning anti-digoxin Fab fragments would not have provided any motivation regarding a Crotalus Fab antivenom. Indeed, the Smith *et. al.* article itself recognizes that the Fab-digoxin complex is cleared by the renal system, stating that Fab fragments "substantially enhance the rate of urinary excretion of digoxin." [Smith *et. al.* at p. 385.] As discussed in detail above, this concentration of the Fab fragments at the kidneys, while desirable for a small molecule like digoxin, would be undesirable for venom toxins. [First Russell Decl. at § 36; Sullivan Decl. ¶ 5(a).] Like Faulstich *et. al.*'s results with α-amatoxin, Fab fragments to Crotalus venom would have been expected to concentrate high molecular weight venom toxins at the kidney, resulting in increased kidney toxicity. Thus, Smith *et. al.* would have not provided any motivation to attempt the claimed invention with a reasonable expectation of success.

In sum, before Appellants' invention, those of ordinary skill in the art did not have a reasonable expectation of success that an antivenom pharmaceutical composition comprising Fab fragments to Crotalus venom would be effective at neutralizing the lethality of the venom of

snake of the Crotalus genus. Obviousness requires that "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not [Appellants'] disclosure," *Vaeck*, 20 U.S.P.Q.2d at 1442, and Appellants have shown that that is not the case here. Despite the long-known problems with the commercially available venom for Crotalus envenomation since 1947, and the well-known fact that smaller immunoglobulin fragments are less immunogenic, those of ordinary skill in the art had not progressed beyond antivenoms comprising the disappointing $F(ab)_2$ fragments to the smaller Fab fragments because they expected Fab fragments to be not just ineffective, but actually more harmful to the patient than no treatment at all.

For all these reasons, any combination of Sullivan *et al.* and Coulter *et al.*, including the addition of Smith *et al.* and evidence from Stedman's Medical Dictionary, would not have taught one of ordinary skill in the art to prepare an antivenom pharmaceutical composition for treating a snakebite victim comprising Fab fragments, wherein the antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the Crotalus genus.

IX. Conclusion

In view of the foregoing Appellants, respectfully request reversal of the two rejections of claims 40-42 and 50 under 35 U.S.C. § 103 and allowance of the pending claims.

If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 that are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 23/2825.

Respectfully submitted,

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APPENDIX

40. An antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier, wherein said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the Crotalus genus.

41. The antivenom pharmaceutical composition of claim 40, wherein an antibody source for said Fab fragments is IgG(T).

42. The antivenom pharmaceutical composition of claim 40, wherein an antibody source for said Fab fragments is polyvalent IgG(T).

50. The antivenom pharmaceutical composition of claim 40, wherein the Fab fragments are equine.